

Serial No. 10/030,188

Reply to Office Action of Aug. 12, 2003

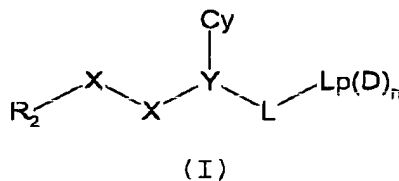
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Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1 (currently amended): A serine protease inhibitor of formula (I):



wherein:

R₂ is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, MeSO₂- or R₁, or the substituents at the 3 or 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j}, and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered

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aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxy carbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that R_2 cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO, CR_{1a} , $C(R_{1a})_2$ or NR_{1a} group, at least one X being C, CO, CR_{1a} or $C(R_{1a})_2$;

each R_{1a} independently represents hydrogen or hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxy carbonyl, alkylaminocarbonyl, alkoxy carbonylamino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

R_1 is as defined for R_{1a} , provided that R_1 is not unsubstituted aminoalkyl;

Y (the α -atom) is a ~~nitrogen atom or a CR_{1b} -CH~~ group;

Cy is a saturated or unsaturated, mono or poly cyclic, ~~homo or heterocyclic~~ homocyclic group, optionally substituted by groups R_{3a} or $R_{3i}X_i$;

each R_{3a} independently is R_{1c} , amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkylimidazolyl, thiazolyl, alkylthiazolyl, alkylloxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S; and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group), or $-OCH_2O-$ which is bonded to two adjacent ring atoms in Cy;

X_i is a bond, O, NH or CH_2 ;

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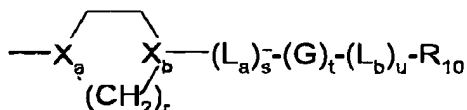
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R_{3i} is phenyl, pyridyl or pyrimidinyl optionally substituted by R_{3a} ; and

~~R_{1b}~~ R_{1c} and R_{1j} are as defined for R_{1a} ;

L is an organic linker group containing 1 to 5 backbone atoms selected from C, N, O and S, or a branched alkyl or cyclic group; and

$Lp(D)_n$ is of the formula:



β^1 in which:

r is 1 or 2;

X_a is CH and X_b is N;

s , t and u are each 0 or 1;

L_a and L_b are each independently selected from a single bond, C=O, O and NR_{1e} , in which R_{1e} is hydrogen or (1-6C)alkyl;

G is (1-6C)alkanediyl; and

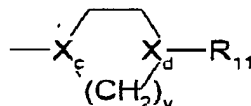
R_{10} is (1-6C)alkyl; (3-6C)cycloalkyl [which is unsubstituted or substituted by (1-6C)alkyl]; indanyl; pyridyl; tetrahydropyranyl; tetrahydrothiopyranyl; phenyl [which is unsubstituted or substituted by one or two R_3 groups [wherein R_3 is hydrogen, hydroxyl, alkoxy, alkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), hydroxyalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, acyloxymethoxycarbonyl, aminoalkyl (optionally substituted by

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hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkylamino (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkyl imidazolyl, thiazolyl, alkyl thiazolyl, alkyl oxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, or haloalkyl}}, pyrrolinyl; or a group of formula:



in which v is 1, 2 or 3; one of X_c and X_d is N and the other is CH or N (provided that when v is 1, X_c and X_d are not both N); and R₁₁ is hydrogen, (1-6C)alkyl or when X_d is CH, hydroxy(1-6C)alkyl; provided that when t is 0, the sum of s and u is 1; when X_b is N, L_a is a bond or C=O; when X_c is N, L_b is a bond or C=O; when X_b and X_c are both N, t is 1; and when (L_a)_s-(G)_t-(L_b)_u represents an alkyl group and X_b and X_c both represent N, the alkyl group contains at least two chain carbon atoms;

or R₁₀ is hydrogen and s, t and u are each 0;

or the compound of formula (I) that is 4-{[4-methoxybenzoyl-D,L-(2-trifluoromethylthiophenyl)-glyciny]aminomethyl}-1-isopropylpiperidine;

but excluding the compound 4-[(3-ethoxybenzoyl-D,L-phenylglyciny]aminomethyl]-1-[4-chlorobenzyl]piperidine;

or a physiologically-tolerable salt thereof.

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2 (currently amended): A serine protease inhibitor according to claim 1, wherein:

B' R_2 is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, $MeSO_2-$ or R_1 , or the substituents at the 3 or 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j} , and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxy, carbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that R_2 cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO, CR_{1a} , $C(R_{1a})_2$ or NR_{1a} group, at least one X being C, CO, CR_{1a} or $C(R_{1a})_2$;

each R_{1a} independently represents hydrogen or hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxy, carbonyl, alkylaminocarbonyl, alkoxy, carbonyl, amino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

R_1 is as defined for R_{1a} , provided that R_1 is not unsubstituted aminoalkyl;

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Y (the α -atom) is a ~~nitrogen atom or a CR_{1b}~~ CH group;

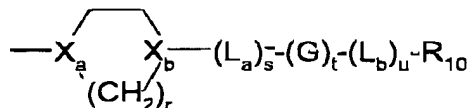
Cy is a saturated or unsaturated, mono or poly cyclic, ~~homocyclic homo or heterocyclic~~ group optionally substituted by groups R_{3a} or phenyl optionally substituted by R_{3a};

each R_{3a} independently is R_{1c}, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkyl imidazolyl, thiazolyl, alkyl thiazolyl, alkyl oxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy or haloalkyl; and

~~R_{1b}~~ R_{1c} and R_{1j} are as defined for R_{1a};

L is an organic linker group containing 1 to 5 backbone atoms selected from C, N, O and S, or a branched alkyl or cyclic group; and

Lp(D)_n is of the formula:



in which:

r is 1 or 2;

X_a is CH and X_b is N;

s, t and u are each 0 or 1;

L_a and L_b are each independently selected from a single bond, C=O, O and NR_{1e}, in which R_{1e} is hydrogen or (1-6C)alkyl;

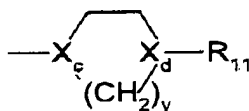
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G is (1-6C)alkanediyl; and

B' R₁₀ is (1-6C)alkyl; (3-6C)cycloalkyl [which is unsubstituted or substituted by (1-6C)alkyl]; indanyl; pyridyl; tetrahydropyranyl; tetrahydrothiopyranyl; phenyl {which is unsubstituted or substituted by one or two R₃ groups [wherein R₃ is hydrogen, hydroxyl, alkoxy, alkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), hydroxyalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, acyloxymethoxycarbonyl, aminoalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkylamino (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkyl imidazolyl, thiazolyl, alkyl thiazolyl, alkyl oxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy or haloalkyl]}, pyrrolinyl; or a group of formula:



in which v is 1, 2 or 3; one of X_c and X_d is N and the other is CH or N, provided that when v is 1, X_c and X_d are not both N; and R₁₁ is hydrogen, (1-6C)alkyl or when X_d is CH, hydroxy(1-6C)alkyl; provided that when t is 0, the sum of s and u is 1; when X_b is N, L_a is a bond or C=O; when X_c is N,

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L_D is a bond or $C=O$; when X_D and X_C are both N, t is 1; and when $(L_A)_S-(G)_T-(L_D)_U$ represents an alkyl group and X_D and X_C both represent N, the alkyl group contains at least two chain carbon atoms,

or a physiologically-tolerable salt thereof.

3 (previously presented): A serine protease inhibitor according to claim 1, wherein R^3 is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, *t*-butyl, pentyl, 2-pentyl, 3-pentyl, isopropylaminomethyl, dimethylamino-methyl, diethylaminomethyl, dimethylaminoethyl, acetyl, hydroxymethyl, hydroxyethyl, carboxy, carboxy(1-5C)alkyl, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl, aminocarbonyl, aminocarbonyl(1-5C)alkyl, methylamino, dimethylamino, ethylamino, formylamino, acetylamino, amino, fluoro, chloro, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, isopropylsulphonyl, methylsulphenyl, 1,2,4-triazol-2-yl, 1,2,4-triazol-4-yl, 1,2,3-triazol-4-yl, 1,3-imidazol-1-yl, 1,3-imidazol-4-yl, tetrazol-1-yl, tetrazol-5-yl, methylsulphonamido, ethylsulphonamido, propylsulphonamido, methylaminosulphonyl, ethylaminosulphonyl, propylaminosulphonyl, aminosulphonyl, trifluoromethoxy, trifluoromethyl and trichloromethyl.

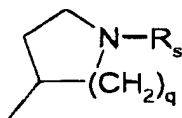
4 (previously presented): A compound according to claim 1 wherein r is 2.

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5 (original): A compound according to claim 1 wherein $Lp(D)_n$ is of the formula:



wherein:

q is 1 or 2;

B¹ R_s is hydrogen, $-(CH_2)_c-R_c$, $-CHReR_f$, or $-CH_2-CHReR_f$ [c is 0, 1 or 2; wherein R_c is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, $CONH_2$, SO_2NH_2 , methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent) and R_e and R_f are independently hydrogen or C_{1-3} alkyl; or $CHReR_f$ is (3-6C)cycloalkyl (which may bear a methyl, ethyl or hydroxymethyl substituent at the 3- or 4-position, provided the substituent is not bonded to the CH group which is bonded to L), tetrahydropyranyl, tetrahydrothiopyranyl, pyrrolidinyl (which may bear a 1-methyl substituent), piperidinyl (which may bear a 1-methyl substituent) (provided that the tetrahydropyranyl, tetrahydrothiopyranyl, pyrrolidinyl and piperidinyl rings are not linked to the piperidin-1,4-diyl group through a ring nitrogen atom or a ring carbon atom adjacent to a ring oxygen, sulfur or nitrogen atom) or indan-2-yl].

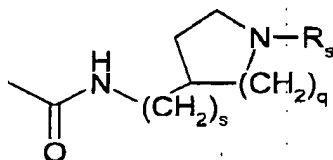
6 (previously presented): A compound according to claim 1 wherein L is $CONH$, CH_2NHCO , $CONHCH_2$, $CONHCH_2CH_2$ or $CON(Me)CH_2$.

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7 (original) A serine protease inhibitor according to claim 2 wherein $-L-Lp(D)_n$ is of the formula:



wherein

q is 1 or 2;

s is 0 or 1; and

B¹ R_s is $-(CH_2)_c-R_c$, $-CHReR_f$, or $-CH_2-CHReR_f$ [wherein c is 1 or 2; R_c is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, $CONH_2$, SO_2NH_2 , methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent) and R_e and R_f are independently hydrogen or C_{1-3} alkyl; or $CHReR_f$ is cyclopentyl (which may bear a methyl, ethyl or hydroxymethyl substituent at the 3- or 4-position), cyclohexyl (which may bear a methyl, ethyl or hydroxymethyl substituent at the 3- or 4-position), tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, pyrrolidin-3-yl (which may bear a 1-methyl substituent), piperidin-4-yl (which may bear a 1-methyl substituent), or indan-2-yl].

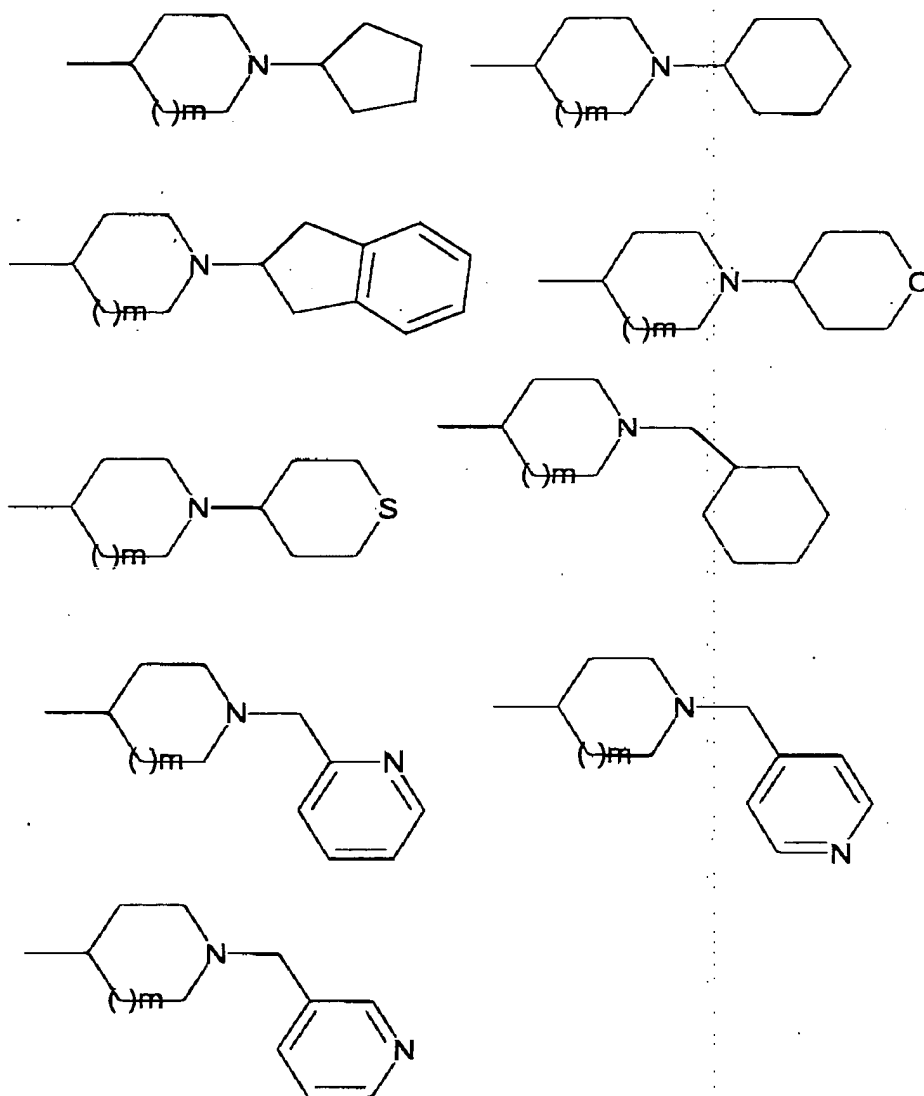
8 (previously presented): A compound according to claim 5 wherein q is 2.

9 (previously presented): A compound according to claim 1 wherein $Lp(D)_n$ is selected from one of the following formulae:

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wherein m represents 0 or 1.

10 (previously presented): A compound according to claim 7 wherein R_5 is selected from: hydrogen, methyl, ethyl, prop-2-yl, but-2-yl, pent-3-yl, hept-4-yl, cyclopentyl, cyclohexyl,

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cyclohexylmethyl, 1-methylpiperidin-4-yl, tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, phenyl, benzyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, pyrid-3-ylmethyl, pyrid-4-ylmethyl and indan-2-yl.

11 (previously presented): A compound according to claim 1 wherein R₂ is phenyl, thien-2-yl, naphthyl, indol-2-yl, indol-6-yl, benzo[b]furan-5-yl, benzo[b]thiophen-2-yl or benzimidazol-2-yl (each of which is optionally substituted as defined in claim 1).

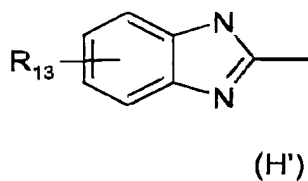
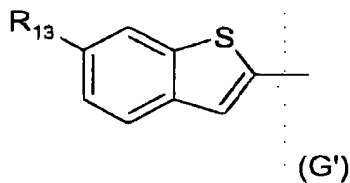
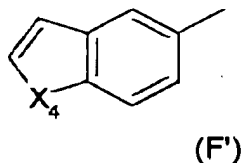
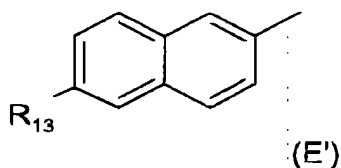
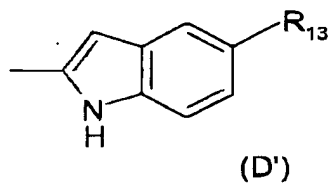
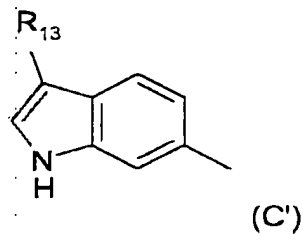
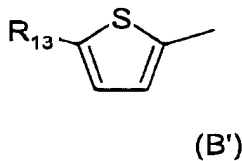
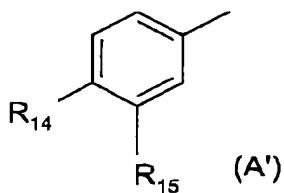
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12 (previously presented): A compound according to claim 11 wherein optional substituents for R₂ are selected from: fluoro, chloro, bromo, iodo, nitro, thiol, difluoromethoxy, trifluoromethoxy, hydrazido, methylhydrazido, amino, cyano, trifluoromethyl, methylthio, vinyl, ethynyl, acetylamino, carboxy, acetoxy, hydroxy, methyl, ethyl, amido (CONH₂), aminomethyl, methoxy and ethoxy.

13 (previously presented): A compound according to claim 1 wherein R₂ is selected from one of the formula (A') to (H'):

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wherein X_4 is O or S, R_{13} is selected from hydrogen, fluoro, chloro or methyl and R_{14} is selected from hydrogen, methyl, ethyl, fluoro, chloro, and methoxy and R_{15} is selected from hydrogen, methyl, fluoro, chloro and amino.

14 (previously presented): A compound according to claim 1, wherein R_2 is 4-methoxyphenyl, 3-amino-4-chlorophenyl, indol-2-yl, 5-chloroindol-2-yl, indol-6-yl, 3-chloroindol-6-yl or 3-

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methyldol-6-yl.

15 (previously presented): A compound according to claim 1 wherein -X-X- is -CONH-.

16 (canceled).

B¹
17 (currently amended): A compound according to claim 1 wherein Cy is an optionally R_{3a} substituted: phenyl, ~~pyridyl~~, ~~thienyl~~, ~~thiazolyl~~, ~~naphthyl~~, ~~piperidinyl~~, ~~furanyl~~, ~~pyrrolyl~~, ~~isoxazolyl~~, ~~isothiazolyl~~, ~~pyrazolyl~~, ~~oxazolyl~~, ~~imidazolyl~~, ~~1,3,4-thiadiazolyl~~, ~~1,3,4-thiadiazolyl~~, ~~pyrimidinyl~~, ~~pridazinyl~~, ~~quinolyl~~, ~~isoquinolyl~~, ~~benzofuryl~~, ~~benzothienyl~~ or cycloalkyl group, or a phenyl group substituted by R_{3i}X_i in which X_i is a bond, O, NH or CH₂ and R_{3i} is phenyl, pyridyl or pyrimidinyl optionally substituted by R_{3a}.

18 (currently amended): A compound according to claim 1 wherein Cy is an optionally R_{3a} substituted: phenyl, ~~pyridyl~~, ~~thienyl~~, ~~thiazolyl~~, ~~naphthyl~~, ~~piperidinyl~~ or cycloalkyl group.

19 (canceled)

20 (canceled)

21 (previously presented): A compound according to claim 1 wherein R_{3a} is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl,

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B¹

ethoxycarbonyl, methylaminocarbonyl, dimethylamino-carbonyl, aminomethyl, CONH₂, CH₂CONH₂, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, bromo, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy, trifluoromethyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, morpholin-1-ylcarbonyl and -OCH₂O- (which is bonded to two adjacent ring atoms in Cy).

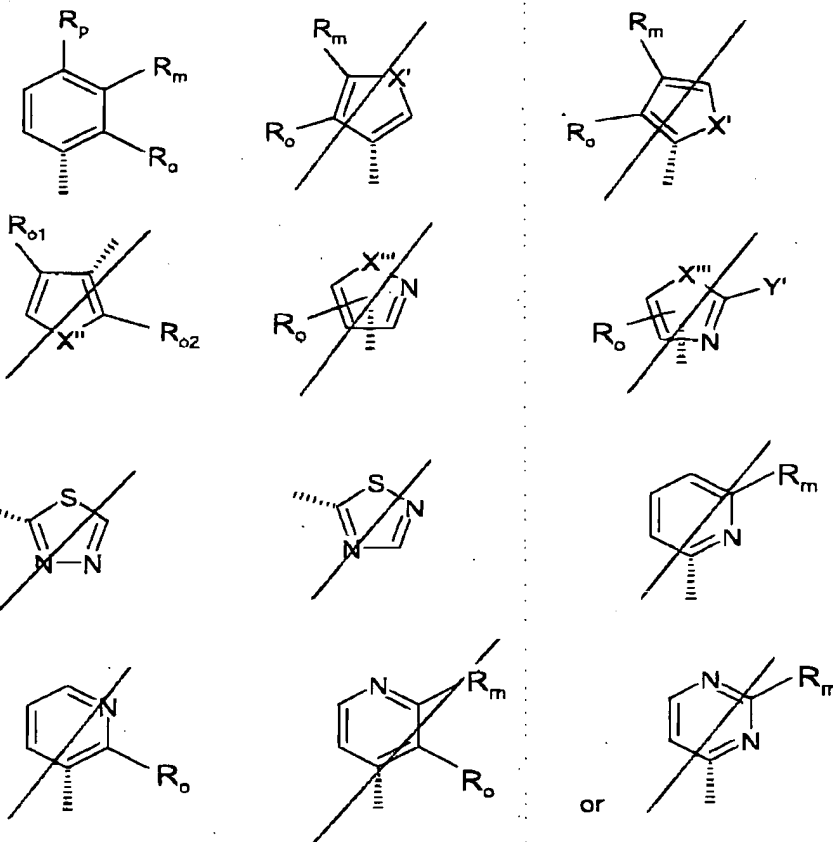
22 (previously presented): A compound according to claim 1 wherein R_{3a} is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylamino-carbonyl, aminomethyl, CONH₂, CH₂CONH₂, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy and trifluoromethyl.

23 (currently amended): A compound according to claim 1 wherein Cy is ~~selected from~~

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wherein:

~~X' is selected from O, S and NMe;~~~~X'' is selected from O and S;~~~~X''' is selected from O, S, NH and NMe;~~~~Y' is selected from hydrogen, amino and methyl;~~

R_o is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphanyl and methylsulphonyl;

R_m is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphanyl, methylsulphonyl, carboxy, methoxycarbonyl and a group of the

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formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group); R_p is selected from hydrogen and fluoro; or

R_o and R_m or R_m and R_p form an $-OCH_2O-$ group; or

R_o and R_m together with the ring to which they are attached form a 5 or 6 membered aryl or heteroaryl ring (wherein the heteroaryl ring contains 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur);

~~one of R_{o1} and R_{o2} is hydrogen and the other is R_o .~~

24 (currently amended): A compound according to claim 1 wherein Cy is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl, 4-carbamoylphenyl, ~~pyrid-2-yl, pyrid-3-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, and naphthyl, isoquinolin-5-yl, isoquinolin-8-yl, quinolin-4-yl, quinolin-5-yl, and quinolin-8-yl.~~

25 (currently amended): A compound as claimed in any one of claims 1-15, 17-18 and 21-24 ~~Claim 15~~, in which the alpha atom in Y ~~is carbon and~~ has the conformation that would result from construction from a D- α -aminoacid $NH_2-CH(Cy)-COOH$ NH_2- ~~$CR_{1b}(Cy)-COOH$~~ where the NH_2 represents part of X-X

26 (previously presented): A pharmaceutical composition, which comprises a compound as claimed in claim 1 together with at least one pharmaceutically acceptable carrier or excipient.

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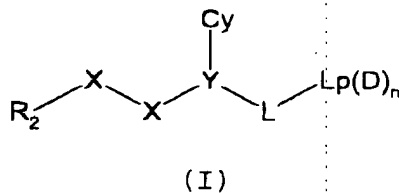
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27 (canceled).

28 (canceled).

29 (currently amended): A method of treatment of a human or non-human animal body to combat a thrombotic disorder, which comprises administering to said body an effective amount of a ~~compound as claimed in claim 1, but including the compound 4~~ ~~[(3-ethoxybenzoyl-D,L-phenylglyciny]aminomethyl]~~ ~~1-[4-chlorobenzyl]piperidine~~ serine protease inhibitor of formula (I):



wherein:

R₂ is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, MeSO₂- or R₁, or the substituents at the 3 or 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy,

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haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j}, and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxy, carbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that R₂ cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO, CR_{1a}, C(R_{1a})₂ or NR_{1a} group, at least one X being C, CO, CR_{1a} or C(R_{1a})₂;

B1 each R_{1a} independently represents hydrogen or hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxy, carbonyl, alkylaminocarbonyl, alkoxy, carbonylamino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

R₁ is as defined for R_{1a}, provided that R₁ is not unsubstituted aminoalkyl;

Y (the α -atom) is a CH group;

Cy is a saturated or unsaturated, mono or poly cyclic, homocyclic group, optionally substituted by groups R_{3a} or R_{3i}X_i;

each R_{3a} independently is R_{1c}, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkylimidazolyl, thiazolyl, alkylthiazolyl, alkyloxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a group of the formula -C(X³)N(R¹¹)R¹² (wherein X³ is O or S; and R¹¹ and R¹² are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or

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morpholino group), or -OCH₂O- which is bonded to two adjacent ring atoms in Cy;

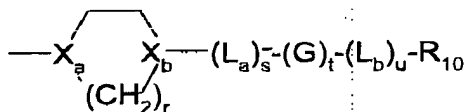
X_i is a bond, O, NH or CH₂;

R_{3i} is phenyl, pyridyl or pyrimidinyl optionally substituted by R_{3a}; and

R_{1c} and R_{1j} are as defined for R_{1a};

L is an organic linker group containing 1 to 5 backbone atoms selected from C, N, O and S, or a branched alkyl or cyclic group; and

Lp(D)_n is of the formula:



in which:

r is 1 or 2;

X_a is CH and X_b is N;

s, t and u are each 0 or 1;

L_a and L_b are each independently selected from a single bond, C=O, O and NR_{1e}, in which R_{1e} is hydrogen or (1-6C)alkyl;

G is (1-6C)alkanediyl; and

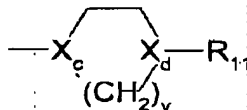
R₁₀ is (1-6C)alkyl; (3-6C)cycloalkyl [which is unsubstituted or substituted by (1-6C)alkyl]; indanyl; pyridyl; tetrahydropyranyl; tetrahydrothiopyranyl; phenyl [which is unsubstituted or substituted by one or two R₃ groups [wherein R₃ is hydrogen, hydroxyl, alkoxy, alkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), hydroxyalkyl (optionally substituted by hydroxy,

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alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkoxyalkyl, alkoxy carbonyl, alkylaminocarbonyl, alkoxy carbonylamino, acyloxymethoxycarbonyl, aminoalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkylamino (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkyl imidazolyl, thiazolyl, alkyl thiazolyl, alkyl oxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, or haloalkyl}}; pyrrolinyl; or a group of formula:



in which v is 1,2 or 3; one of X_c and X_d is N and the other is CH or N (provided that when v is 1, X_c and X_d are not both N); and R₁₁ is hydrogen, (1-6C)alkyl or when X_d is CH, hydroxy(1-6C)alkyl; provided that when t is 0, the sum of s and u is 1; when X_b is N, L_a is a bond or C=O; when X_c is N, L_b is a bond or C=O; when X_b and X_c are both N, t is 1; and when (L_a)_s-(G)_t-(L_b)_u represents an alkyl group and X_b and X_c both represent N, the alkyl group contains at least two chain carbon atoms;

or R₁₀ is hydrogen and s, t and u are each 0;

or the compound of formula (I) that is 4-{[4-methoxybenzoyl-D,L-(2-trifluoromethylthiophenyl)-glyciny]aminomethyl}-1-isopropylpiperidine;
or a physiologically-tolerable salt thereof.

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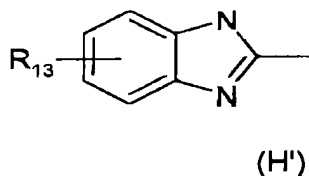
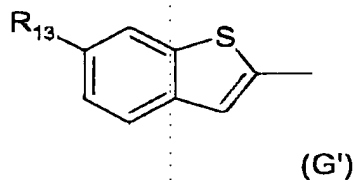
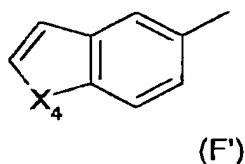
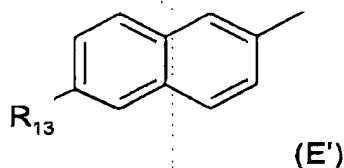
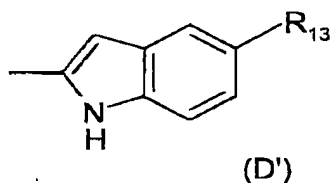
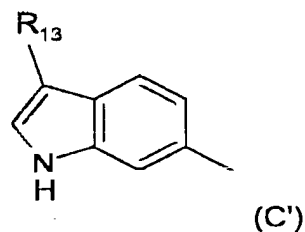
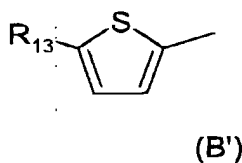
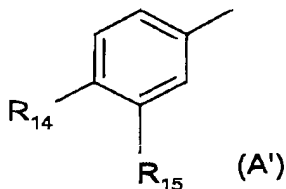
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30 (canceled).

31 (canceled).

32 (currently amended): A compound according to Claim 1
wherein:

R₂ is selected from one of the formula (A') to (H'):



wherein X₄ is O or S, R₁₃ is selected from hydrogen, fluoro, chloro or methyl and R₁₄ is selected from hydrogen, methyl,

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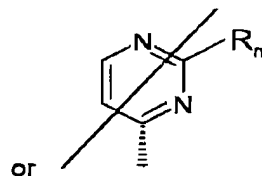
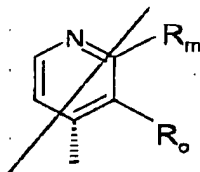
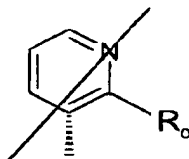
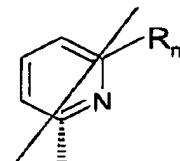
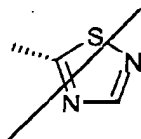
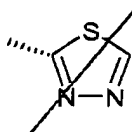
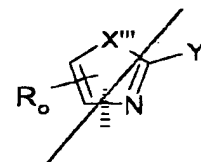
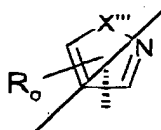
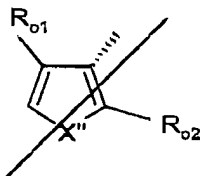
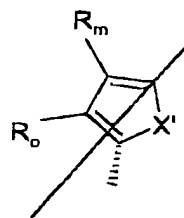
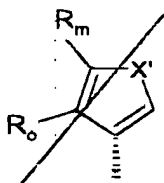
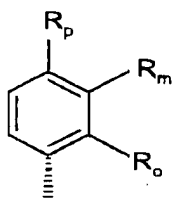
ethyl, fluoro, chloro, and methoxy and R_{15} is selected from hydrogen, methyl, fluoro, chloro and amino;

X-X represents CONH;

Y (the α -atom) is CH and has the conformation that would result from construction from a D- α -aminoacid

$\text{NH}_2\text{-CH}(\text{Cy})\text{-COOH}$ ~~$\text{NH}_2\text{-CH}(\text{Cy})\text{-COOH}$~~ where the NH_2 represents part of X-X;

Cy is ~~selected from~~



wherein:

~~X' is selected from O, S and NMe,~~

~~X'' is selected from O and S,~~

~~X''' is selected from O, S, NH and NMe,~~

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~~Y' is selected from hydrogen, amino and methyl,~~

R_O is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphanyl and methylsulphonyl;

R_M is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphanyl, methylsulphonyl, carboxy, methoxycarbonyl and a group of the formula -C(X³)N(R¹¹)R¹² (wherein X³ is O or S and R¹¹ and R¹² are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group);

R_P is selected from hydrogen and fluoro; or

R_O and R_M or R_M and R_P form an -OCH₂O- group; or

R_O and R_M together with the ring to which they are attached form a 5 or 6 membered aryl or heteroaryl ring (wherein the heteroaryl ring contains 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur);

~~one of R_{O1} and R_{O2} is hydrogen and the other is R_O; and~~

L is CONH, CH₂NHCO, CONHCH₂, CONHCH₂CH₂ or CON(Me)CH₂.

33 (currently amended): A compound according to Claim 32 wherein

R₂ is 4-methoxyphenyl, 3-amino-4-chlorophenyl, indol-2-yl, 5-chloroindol-2-yl, indol-6-yl, 3-chloroindol-6-yl or 3-methylindol-6-yl;

Cy is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl, 4-carbamoylphenyl and ~~pyrid-2-yl, pyrid-3-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, naphthyl,~~

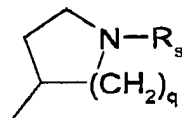
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~~isoquinolin-5-yl, isoquinolin-8-yl, quinolin-4-yl, quinolin-5-yl, and quinolin-8-yl; and~~

Lp(D)_n is of the formula:



wherein:

q is 1 or 2;

B1
 R_s is hydrogen, -(CH₂)_c-R_c, -CHR_eR_f, or -CH₂-CHR_eR_f [c is 0, 1 or 2; wherein R_c is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, CONH₂, SO₂NH₂, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent) and R_e and R_f are independently hydrogen or C₁₋₃alkyl; or CHR_eR_f is (3-6C)cycloalkyl (which may bear a methyl, ethyl or hydroxymethyl substituent at the 3- or 4-position, provided the substituent is not bonded to the CH group which is bonded to L), tetrahydropyranyl, tetrahydrothiopyranyl, pyrrolidinyl (which may bear a 1-methyl substituent), piperidinyl (which may bear a 1-methyl substituent) (provided that the tetrahydropyranyl, tetrahydrothiopyranyl, pyrrolidinyl and piperidinyl rings are not linked to the piperidin-1,4-diyl group through a ring nitrogen atom or a ring carbon atom adjacent to a ring oxygen, sulfur or nitrogen atom) or indan-2-yl].

34 (currently amended): A compound according to Claim 2

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wherein

R₂ represents:

(i) phenyl optionally being substituted in the 3 and/or 4 position by fluoro, chloro, bromo, iodo, nitro, difluoromethoxy, trifluoromethoxy, amino, cyano, trifluoromethyl, methylthio, vinyl, carboxy, acetoxy, MeSO₂-, hydroxy, methoxy, ethoxy, methyl, methoxycarbonyl, methylamino, ethylamino or amido, and optionally substituted at the 6 position by amino, hydroxy, fluoro, methoxycarbonyl, cyano or aminomethyl;

B¹ (ii) naphth-2-yl optionally substituted at the 6, position by hydroxy and optionally substituted at the 3 position by amino or hydroxy;

(iii) isoquinolin-7-yl, indol-5-yl, indol-6-yl, indazol-5-yl, indazol-6-yl, benzothiazol-6-yl or benzisoxazol-5-yl optionally substituted at the 3 position by chloro, bromo, amino, methyl or methoxy;

(iv) benzimidazol-5-yl or benzothiazol-6-yl optionally substituted at the 2 position by amino;

(v) thien-2-yl or thien-3-yl optionally substituted at the 4 or 5 position by methylthio, methyl or acetyl;

(vi) 3,4-methylenedioxyphenyl, 2,3-dihydroindol-6-yl, 3,3-dichloro-2-oxo-indol-6-yl or 1-methyl-3-aminoindazol-5-yl;

(vii) benzothiazol-2-yl, imidazo[1,2-a]pyrimidin-2-yl or tetrahydroimidazo[1,2-a]pyrimidin-2-yl;

(viii) pyrazol-2-yl substituted at the 5 position by methyl;

(ix) pyrid-2-yl optionally substituted at the 6 position by chloro;

(x) pyrid-3-yl optionally substituted at the 4 position by chloro;

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(xi) benzofur-2-yl optionally substituted at the 3 position by chloro, methyl or methoxy, at the 5 or 6 position by methyl and at the 6 position by methoxy;

(xii) indol-2-yl optionally substituted on the indole nitrogen atom by methyl and optionally substituted at the 5 or 6 position by fluoro, chloro, bromo, methyl or methoxy;

(xiii) indol-6-yl substituted at the 5 position by chloro, fluoro or hydroxy and optionally substituted at the 3 position by chloro or methyl; or

31 (xiv) benzo[b]thiophen-2-yl optionally substituted at the 3 position by fluoro, chloro or methyl, and optionally substituted at the 5 or 6 position by fluoro, chloro, methyl, hydroxy, or methoxy;

X-X represents CONH;

Y (the α -atom) is CH and has the conformation that would result from construction from a D- α -aminoacid

NH₂-CH(Cy)-COOH ~~NH₂-CH(Cy)-COOH~~ where the NH₂ represents part of X-X;

Cy is an optionally R_{3a} substituted phenyl, ~~pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl~~ or cycloalkyl group;

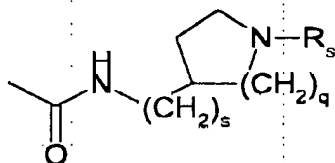
R_{3a} is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylamino-carbonyl, aminomethyl, CONH₂, CH₂CONH₂, acetamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl,

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trifluoromethoxy and trifluoromethyl; and

-L-Lp(D)_n is of the formula:

wherein

q is 1 or 2;

s is 0 or 1; and

R_s is -(CH₂)_c-R_c, -CHR_eR_f, or -CH₂-CHR_eR_f [wherein c is 1 or 2; R_c is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, CONH₂, SO₂NH₂, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent) and R_e and R_f are independently hydrogen or C₁₋₃alkyl; or CHR_eR_f is cyclopentyl (which may bear a methyl, ethyl or hydroxymethyl substituent at the 3- or 4-position), cyclohexyl (which may bear a methyl, ethyl or hydroxymethyl substituent at the 3- or 4-position), tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, pyrrolidin-3-yl (which may bear a 1-methyl substituent), piperidin-4-yl (which may bear a 1-methyl substituent), or indan-2-yl].

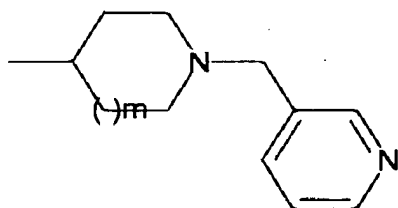
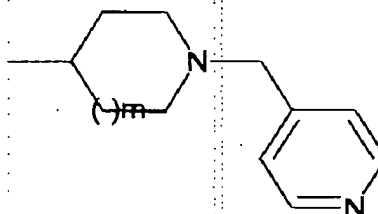
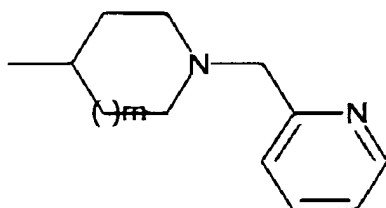
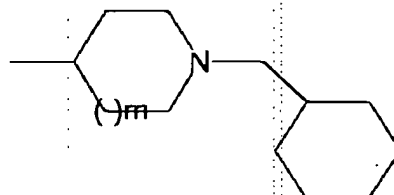
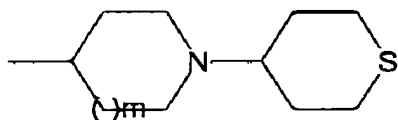
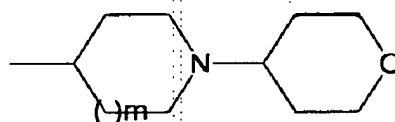
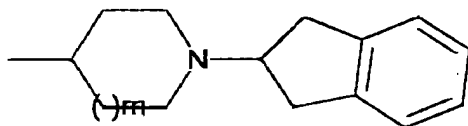
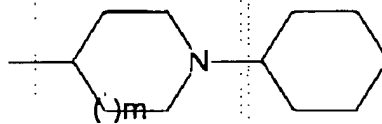
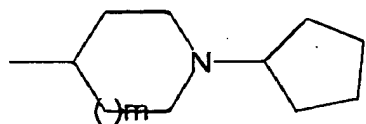
35 (previously presented) A compound according to Claim 34 wherein

Lp(D)_n is selected from one of the following formulae:

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wherein m represents 0 or 1.

36 (new): A compound according to claim 1 wherein R_{1a} represents hydrogen.